

# Infectious Etiologies of Chronic Diseases: A Spectrum of Proof, Opportunities & Challenges



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National Center for Infectious Diseases

# Infectious Etiologies of Chronic Diseases

## DEFINITION

- Sudden insult leaves permanent deficits (e.g., Polio)
- Outcome of infection predisposes to chronic sequelae (e.g., lung disease after pre-term birth)
- **Microbe causes chronic illness and disability through progressive pathology**

# Infectious Etiologies of Chronic Diseases

## EXAMPLE CAUSAL ASSOCIATIONS

1958	<i>Schistosoma</i> spp.	Bladder cancer
1964	Epstein-Barr virus	Burkitt's lymphoma
1975	Hepatitis B virus	Hepatocellular carcinoma
1984	<i>Helicobacter pylori</i>	Duodenal & gastric ulcers
1987	Human papillomavirus	Cervical cancer
1989	Hepatitis C virus	[ Chronic liver disease Hepatocellular carcinoma Mixed cryoglobulinemia
1989		
1990		
1991	KSHV/ human herpesvirus 8	Kaposi sarcoma
1992	<i>Tropheryma whippelii</i>	Whipple's disease

# Infectious Etiologies of Chronic Diseases

## SPECTRUM

- Syndromes & Organ systems

# Infectious Etiologies of Chronic Diseases

## SPECTRUM

➤ Syndromes & Organ systems

➤ Pathogens

bacteria  
parasites  
prions  
viruses

# Infectious Etiologies of Chronic Diseases

## SPECTRUM

➤ Syndromes & Organ systems

➤ Pathogens

bacteria  
parasites  
prions  
viruses

➤ Triggers & outcomes

1 microbe → >1 syndrome  
>1 microbe → 1 outcome

# Infectious Etiologies of Chronic Diseases

## SPECTRUM OF TIMING

INFECTION



**sudden, permanent sequelae**

# Infectious Etiologies of Chronic Diseases

## SPECTRUM OF TIMING

INFECTION



**sudden, permanent sequelae**

**progressive disease**



# Infectious Etiologies of Chronic Diseases

## SPECTRUM OF TIMING

INFECTION



**sudden, permanent sequelae**

**progressive disease**

**immune process**

**symptomatic disease**

# Infectious Etiologies of Chronic Diseases

## SPECTRUM OF TIMING

INFECTION



**sudden, permanent sequelae**

**progressive disease**

**immune process**

**symptomatic disease**

**persistent infection**

**symptomatic disease**

# Infectious Etiologies of Chronic Diseases

## **SPECTRUM of PROOF**

- Proven causality
- Strong evidence
- Speculation

# Infectious Etiologies of Chronic Diseases

## Examples: WELL-RECOGNIZED ASSOCIATIONS

### *"Classics"*

Polio

Polio virus

Trachoma

*Chlamydia trachomatis*

Chagas cardiomyopathy

*Trypanosoma cruzi*

### *Chronic Infection or Disease Process*

Cervical cancer

Human papillomavirus

CLD, Liver cancer

Hepatitis B and C viruses

Lyme arthritis

*Borrelia burgdorferi*

Peptic ulcer disease

*Helicobacter pylori*

Whipple's disease

*Tropheryma whippelii*

Bladder cancer

*Schistosoma haematobium*

# Infectious Etiologies of Chronic Diseases

Examples: ESTABLISHED or STRONG ASSOCIATIONS

## *Sequelae of Acute Event or Intra-partum Infection*

Hearing loss

Cytomegalovirus (CMV)

## *Chronic Infection or Disease Process*

Cryoglobulinemia

Hepatitis C virus

Gastric cancer

*Helicobacter pylori*

Neuroborreliosis

*Borrelia burgdorferi*

Reactive arthritis

Enteric bacteria,  
*Chlamydia trachomatis*

Uveitis, Retinitis

*Borrelia burgdorferi*  
*Toxoplasma gondii*

Vasculitis

HBV, HCV

# Infectious Etiologies of Chronic Diseases

## Examples: POTENTIAL to SPECULATIVE ASSOCIATIONS

### *Sequelae of Acute Event or Intra-partum Infection*

Atherothrombosis

*Chlamydia pneumoniae*, CMV

Pre-term birth sequelae  
(neurologic, pulmonary)

*Ureaplasma urealyticum*

### *Chronic Infection or Disease Process*

Atherosclerosis

*Chlamydia pneumoniae*

Diabetes mellitus

Enteroviruses/Coxsackie B virus

Inflammatory bowel  
disease

*Mycobacterium avium* subsp.  
*paratuberculosis*, *Yersinia*,  
luminal bacteria

Obsessive-compulsive  
disorders (PANDAS)

Group A *Streptococcus*

Lupus

Epstein-Barr virus/Viruses

# Infectious Etiologies of Chronic Diseases

## CAUSAL

### *Helicobacter pylori* in Peptic Ulcer Disease

#### Analytic Tool

#### Strength Of Association

Tissue (ulcer) – histology

+ + + +

Human challenge

+ + + +

Culture

+ + +

PCR – strain identification

+ + + +

Virulence factors – Ab, PCR

+ +

Treatment trials

+ + + +

Urea breath test

+ + + (+)

Serology, stool antigen detection

+ + +

Animal models

+ +

# Infectious Etiologies of Chronic Diseases

## CAUSAL

### Hepatitis B virus in CLD, Liver Cancer

#### Analytic Tool

#### Strength Of Association

Epidemiology and time-space

+ + +

Serology – HBsAg  
(HBeAg, anti-HBc)

+ + + +

Serum viral assays

+ + (+)

Tissue – PCR, IHC

+ + + +

Vaccine & other prevention

+ + + +

Treatment trials

+ + +

Animal model

+ + +



# Infectious Etiologies of Chronic Diseases

## CAUSALITY NOT PROVEN

### *Chlamydia pneumoniae* in Atherosclerotic CVD

#### Analytic Tool

#### Strength Of Association

Serology

+ +

PCR on PBMC

+

Tissue (atheroma) – IHC, ICC

+ + (+)

Tissue (atheroma) – PCR

+ + (+)

Culture

+

Animal models

+ +

Treatment trials

+

# Infectious Etiologies of Chronic Diseases

**INFECTIOUS  
DISEASE**

**CHRONIC  
DISEASE**

# **Infectious Etiologies of Chronic Diseases**

## **PREVENTION OPPORTUNITY**

**90 million with Chronic Illness and Disability  
In the U.S.**

# Infectious Etiologies of Chronic Diseases

## PREVENTION OPPORTUNITY

**90 million with Chronic Illness and Disability**

suppose

**10%**

attributable to  
Infectious Diseases

# Infectious Etiologies of Chronic Diseases

## PREVENTION OPPORTUNITY

**90 million with Chronic Illness and Disability**

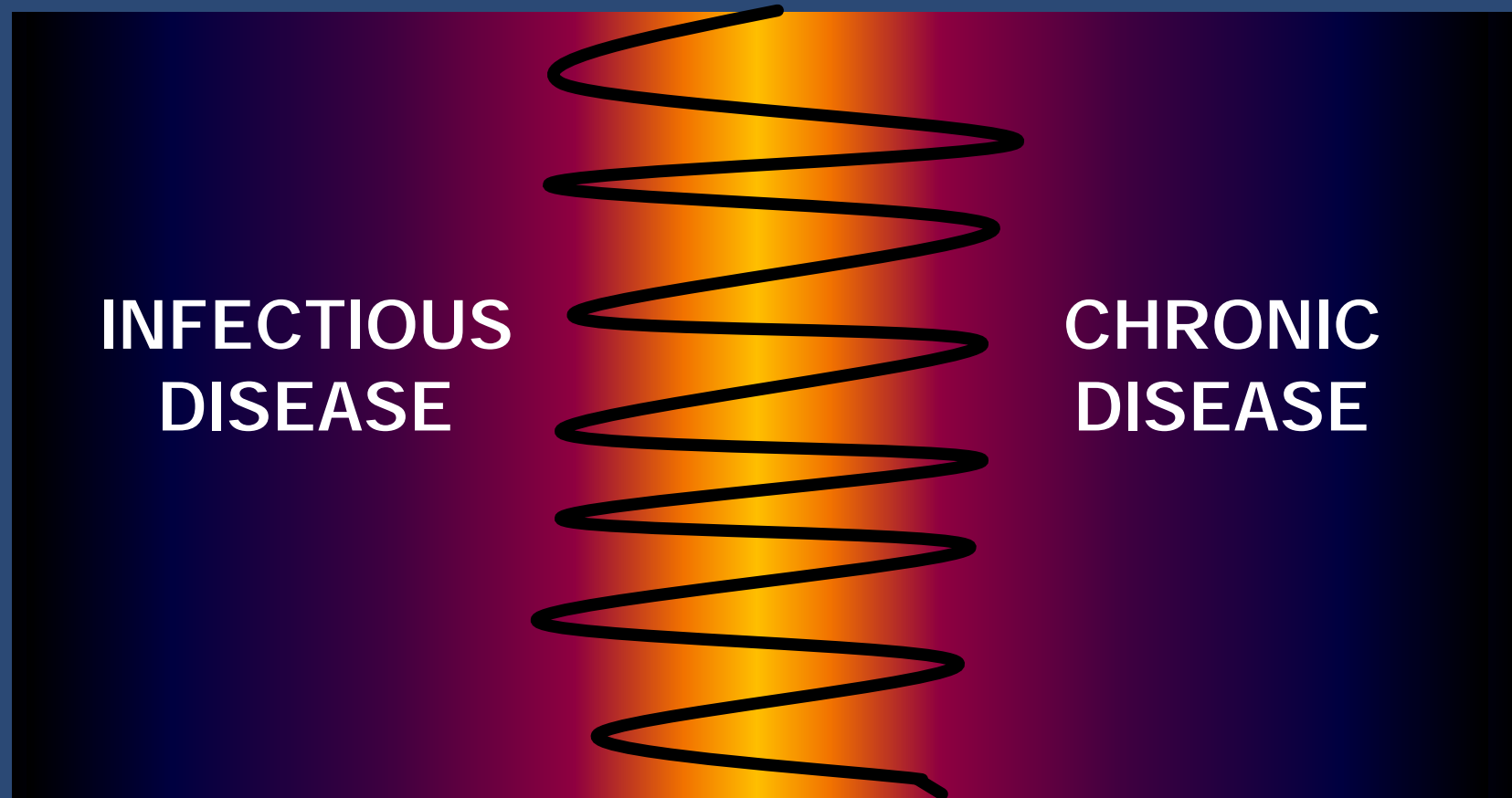
suppose

**10%**

attributable to  
Infectious Diseases

**Impact 9 million people in U.S.**

# Infectious Etiologies of Chronic Diseases



# Infectious Etiologies of Chronic Diseases

## POTENTIAL FOR PREVENTION

### Peptic Ulcer Disease

1980



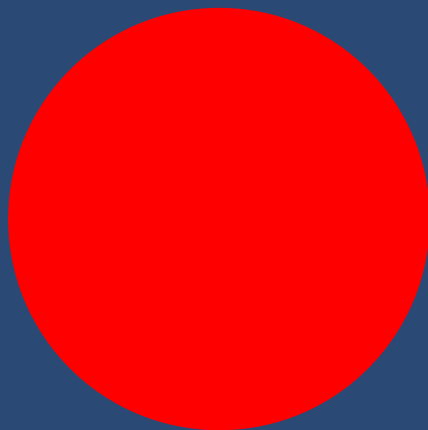
Stress, diet, acid, etc.

# Infectious Etiologies of Chronic Diseases

## POTENTIAL FOR PREVENTION

### Peptic Ulcer Disease

1980



Stress, diet, acid, etc.

1984

*Helicobacter  
pylori*

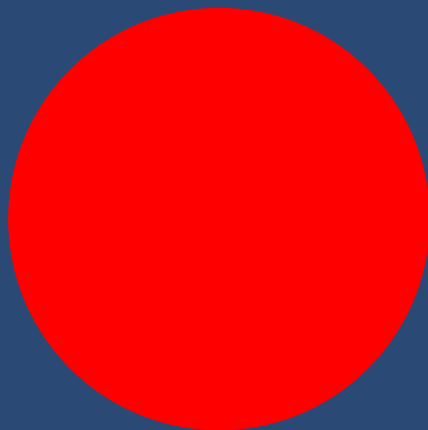


# Infectious Etiologies of Chronic Diseases

## POTENTIAL FOR PREVENTION

### Peptic Ulcer Disease

1980

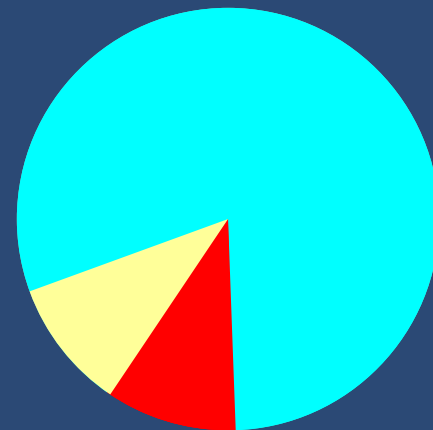


Stress, diet, acid, etc.

1984

*Helicobacter pylori*

2001



*H. pylori*

# Infectious Etiologies of Chronic Diseases

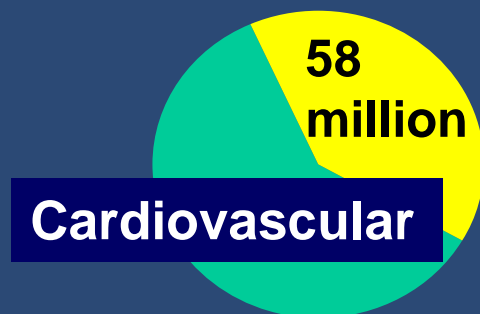
## FUTURE OPPORTUNITIES?

**Disease**

**Hypothetical  
Infectious Etiology**

**Lives  
Saved**

**Disease  
Minimized**



**58  
million**

**Cardiovascular**

**10%**

**96,000**

**6 million**

# Infectious Etiologies of Chronic Diseases

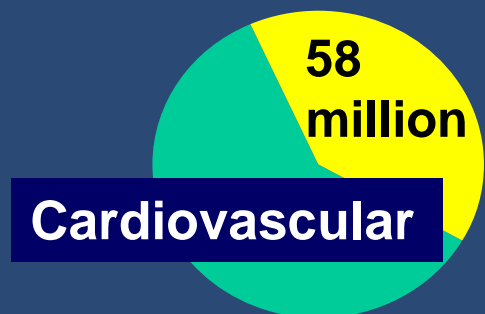
## FUTURE OPPORTUNITIES?

Disease

Hypothetical  
Infectious Etiology

Lives  
Saved

Disease  
Minimized



10%

96,000

6 million



20%

2.8 million

# **Infectious Etiologies of Chronic Diseases**

## **HURDLES AND CHALLENGES**

- **Recognize associations early**
- **Detect causal agents**
- **Identify populations at risk for**
  - Infection
  - Chronic outcome
- **Determine pathogen-specific attributable fraction**
- **Assess long-term impact**
  - Disability prevalence
  - Microbe eradication, antimicrobial resistance

# Infectious Etiologies of Chronic Diseases

## TECHNICAL CHALLENGES

- Ubiquitous agents
- “New” and “old” microbes – new sites
- Multiple agents – ONE outcome
- ONE microbe – multiple outcomes
- Multifactorial disease

# Infectious Etiologies of Chronic Diseases

## MORE TECHNICAL CHALLENGES

- **Exposure-disease interval**  
(agent may have cleared)
- **Technology**
  - Culture methods (improved)
  - Sensitive and specific detection tools
  - Validated assays
  - Distinguishing active, latent & past infection

# Infectious Etiologies of Chronic Diseases

## EVALUATION CHALLENGES IN THE U.S.

- **Heterogeneity of U.S. population**
  - Geographic diversity
  - Racial/ethnic diversity
- **Migration**
- **Changing epidemiology**
- **Diverse environmental exposures**

# Infectious Etiologies of Chronic Diseases

## PROGRESS REQUIREMENTS

- **Uniform case definitions**
- **Networks of populations and laboratories**
- **Prospective collection and storage**
  - Appropriate specimens & appropriate collection
- **Careful interpretation of data**
  - Molecular detection <sup>1</sup> causality
  - Common exposures → high prevalence in all
  - IgG serology = a past exposure



# **Infectious Etiologies of Chronic Diseases**

## **LABORATORY PROGRESS REQUIREMENTS**

- **Standardized, reproducible diagnostic tools**
- **Specific and sensitive assays, validated in tissues under study**
- **Validation against “gold standard”**
- **Assays that differentiate between past and current infection**
- **High throughput assays?**

# Infectious Etiologies of Chronic Diseases

**INFECTIOUS  
DISEASE**

**CHRONIC  
DISEASE**

# Infectious Etiologies of Chronic Diseases

## PREVENTION OPPORTUNITY

Potential among 90 million with Chronic Diseases?

**INFECTIOUS DISEASE**



**AVOIDABLE FRACTION  
of  
CHRONIC DISEASE**

### PREVENTION

Evidence

Diagnostic tools

Exposure

Antimicrobial therapy

Vaccines